Medication Management at End of Life

Molly Curran, PharmD
February 9, 2016
PGY2 Critical Care Pharmacy Resident
Department of Pharmacy, University Health System, San Antonio, TX
Division of Pharmacotherapy, The University of Texas at Austin, College of Pharmacy
Pharmacotherapy Education and Research Center, University of Texas Health Science Center at San Antonio

Disclosures

I acknowledge that I have no actual or potential conflicts of interest or relevant financial relationships with any commercial interest in relation to this CE.

Pharmacist Learning Objectives:

- To describe the role of medication in managing end of life symptoms
- To explain medication classes important for medical management during end of life care
- To formulate evidence based recommendations for managing patient symptoms at end of life

Pharmacy Technician Objectives:

- To recognize the common medications used in end of life patient care
- To describe the administration routes for medications used in palliative care
- To convert opioid equivalencies for various analgesic medications
Goals for Patient Care:

Rule of Double Effect

- Alleviate physical and emotional symptoms
- Achieve the best possible quality of life (QoL)

Intended effect

Unintended effect

- Relieves discomfort or suffering
- Hastens death?

Unjustified Fears of Double Effect

- Studies evaluating adequate pain control at end of life:
  - No difference in survival
- Studies evaluating the use of sedation at end of life:
  - No significant differences in survival
  - One study favored sedation
- Use symptom relief as means of evaluation

End of Life Decisions

- Meet the needs of patient and family
- May address multitude of concerns about care:
  - Stopping unnecessary interventions
  - Ventilator withdrawal and extubation
  - Aggressive or unnecessary medical therapy
  - Nutrition
- Provide emotional and spiritual support to prepare or plan for patient death
Health Provider Communication

Considerations

Spiritual needs
Plan
Family
Goals of Care
Patient-Centered
Caregivers

Imminently Dying: Prioritizing Comfort

- Prepare for transition to comfort care
  - Stop non-essential drugs
  - Convert medications aimed at comfort to alternative access routes
    - Subcutaneous, topical, parenteral, rectal
  - Providing support for family, friends, caregivers
- Address symptoms at end of life
  - Anticipatory medication orders


What are examples of medications that may be stopped for comfort care patients?

- A. Atorvastatin
- B. Lisinopril
- C. Phenytoin
- D. Estradiol
Medical Symptom Management

End of Life Symptoms

- Pain
- Delirium and anxiety
- Terminal Secretions
- Dyspnea

End of Life: Pain Management

- Many patients die with treatable pain
  - Up to 80%
- Minimize iatrogenic sources of pain
- Use patient self-report or validated tools for assessing
  - Behavioral Pain Scale in ICU
  - Critical Care Pain Observational Tool
  - Nonverbal Pain Scale

References:
**Pain Scale Assessment**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No pain</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Slight or mild discomfort</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderate discomfort</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>痛苦 (Slight-to-moderate pain)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Severe pain</td>
<td></td>
</tr>
</tbody>
</table>

**Strategy for Pain Management**

Adapted from Liverpool Care Pathway

1. **Pain?**
   - Present
     - Controlled?
       - Yes
         - Continue current regimen
       - No
         - Uncontrolled?
           - Yes
             - If opioid naïve: Start PRN Morphine 2-4 mg q 15 min to assess usage
           - No
             - If opioid tolerant: Review current analgesia and increase by 25-100% depending on severity of pain

2. **Take Home Point #1:** If pain well controlled, consider continuing current regimen or using equi-analgesic dose.
Opioid Metabolism: Focus on Morphine

When administered orally, undergoes 1st pass metabolism to produce:
- Active metabolite: Morphine-6-glucuronide
- Inactive metabolite: Morphine-3-glucuronide

Contributes to neurotoxicity

All opioids undergo hepatic metabolism
Metabolites are renally cleared
Consider dose reduction/decreased frequency if side effects

Pharmacokinetics: Sublingual Morphine

<table>
<thead>
<tr>
<th>McIntyre et al.</th>
<th>Pannuti et al.</th>
<th>Weinberg et al.</th>
<th>Osborne et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
</tr>
<tr>
<td>Dose: 10 mg</td>
<td>Dose: 10 mg</td>
<td>Dose: 10 mg</td>
<td>Dose: 23.7 mg</td>
</tr>
<tr>
<td>Chronic</td>
<td>Advanced</td>
<td>Healthy patients</td>
<td>Healthy patients</td>
</tr>
<tr>
<td>Retained: 5 min</td>
<td>Retained: 3 min</td>
<td>Retained: 10 min</td>
<td>Retained until</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mean bioavailability: 81% (70-100%)</td>
<td>No statistically significant differences</td>
<td>Mean bioavailability: 9 ± 11.9%</td>
</tr>
<tr>
<td>MacIntosh</td>
<td>Mean: 100%</td>
<td>Mean: 100%</td>
<td>Mean: 100%</td>
</tr>
<tr>
<td>Measured</td>
<td>Measured</td>
<td>Measured</td>
<td>Measured</td>
</tr>
<tr>
<td>Morphinol</td>
<td>Morphinol</td>
<td>Morphinol</td>
<td>Morphinol</td>
</tr>
<tr>
<td>absorption: 23%</td>
<td>absorption: 23%</td>
<td>absorption: 23%</td>
<td>absorption: 23%</td>
</tr>
<tr>
<td>No statistically significant difference from PO morphine (21.5% v. 20% bioavailability)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Alternative Routes: Sublingual Opioids

Advantages:
- Rapidity of onset
- Bypass 1st pass metabolism
- Intensity/duration analgesia
- Smaller side effect profile
- Non-invasive profile
- Ease of administration

Disadvantages:
- Unpalatable
- Burning sensation
- Need to retain medication for minutes

Pharmacodynamics: Sublingual Morphine

Pannuti et al., n = 8
- Intervention: Oral morphine titrated to effect over 5 weeks
- Outcomes: Mean pain reduction (0-10 VAS): 7.8 to 2.7
- Note: Statistically significant advantages
- Rapidity/Intensity of effect
- Non-ophthalmic evaluation

Engelhardt and Crawford, n = 14
- Intervention: Oral morphine solution
- Outcomes: Average pain score (0-5 rating scale)
- SL: 2.3 ± 0.5
- IV: 2.5 ± 0.6

Population: Advanced cancer
- Dose: 0.1 mg/kg solution

Population: Pediatric surgical patients
- Dose titrated to effect
- Interval: Every 4 hours as needed
- Over 5 weeks

Outcomes:
- Mean pain reduction (0-10 VAS): 7.8 to 2.7
- Average pain scores (0-5 rating scale)
  - SL route: 2.3 ± 0.5
  - IV route: 2.5 ± 0.6

Misc: Statistically significant advantages include:
- Rapidity/intensity of effect
- Nonophthalmic evaluation

All patients received concurrent NSAID therapy which may confound results.

Alternative Routes: Sublingual Opioids

- Other opioids have been studied for sublingual administration:
  - Methadone
  - Fentanyl
- SL bioavailability reported is highly variable

Take Home Point #2: If using SL opioids, avoid doses greater than 2 mL because may leak out of sublingual space


What is the equivalent dose of 10mg IV morphine in mcg of IV fentanyl?

- A. 30 mg
- B. 30 mcg
- C. 100 mcg
- D. 1000 mcg
**Alternative Routes: Rectal Opioids**

- Highly bioavailable absorption in lower rectum → bypass 1st pass metabolism
- Upper rectum absorption undergoes 1st pass metabolism
- Dose similar to oral opioids due to anastomoses
- Any immediate release tablet or solution can be given rectally

**Take Home Point #3:** May give IR opioid tablets/solution/parenteral solution (<60 mL) per rectum if PO route compromised

---

**Alternative Routes: Subcutaneous Opioids**

- May be administered continuously or as needed
- Conversion ratio from IV:SubQ not well established
  - Morphine appears to be 1:1
- Adverse effects include skin irritation, itching, site bleeding
  - Change needle if occurs

**Take Home Point #4:** SubQ tissue allows for absorption of up to 3mL/hr, so consider intrinsic potency of opioid if using this route

---

**Alternative Routes: Transdermal Fentanyl**

- Therapeutic blood levels achieved 13-24 hours after patch removal
- Continue to release drug for up to 24 hours after removal
- May not be sufficient means of pain control for patient in last hours
- Absorption effected by fevers/cachexia
What are alternative routes you can consider in patients without IV access?

A. Subcutaneous
B. Sublingual
C. Transdermal
D. Rectal
E. All of the Above

End of Life: Anxiety and Delirium

- State of apprehension and fear
- Delirium
- Hyper- or hypo-active
- "Terminal agitation"
- No reversible causes present
- May indicate distress:
  - Physical
  - Psychological
  - Existential

End of Life Symptoms

- Pain
- Delirium and anxiety
- Terminal secretions
- Dyspnea

Considerations in Terminal Delirium

- Check medication list:
  - Anti-cholinergics
  - Sedatives
  - Hypnotics
  - Opioids
- Consider other etiologies
  - Withdrawal
  - CNS involvement
  - Metabolic derangements
- Neuroleptics are drugs of choice for treatment:
  - Haloperidol
  - Clozapine
  - Quetiapine
  - Risperidone
- Scant data for atypical agents
- QTc interval - consider risks and benefits
- Benzodiazepines (BZD) may precipitate paradoxical response

Anxiety in Imminent Death

- Common in patients facing life-threatening illnesses
- Address and identify reversible causes
  - Drugs: corticosteroids, stimulants, etc.
- BZD monotherapy for patients with days to weeks
- For patients with months, antidepressants are preferred
- Consider adjunctive BZD for first weeks of therapy
- Consider rebound anxiety in patients previously on oral BZD

Practical Considerations: Benzodiazepine Therapy

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Equivalent Oral Dose (mg)</th>
<th>Half-Life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.15</td>
<td>6-12</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1</td>
<td>10-20</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25-1.0</td>
<td>16-30</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>5</td>
<td>20-100</td>
</tr>
</tbody>
</table>

Take Home Point #5: If patient previously on BZD, consider equi-potent dosing if changing route/drug (PR, IV, SubQ)
End of Life Symptoms

- Pain
- Delirium and anxiety
- Terminal secretions
- Dyspnea

End of Life: Terminal Secretions

- Lose ability to clear/nasal/oral secretions
- Decline of gag reflex/reflexive clearing
- Accumulation of tracheobronchial tree secretions
- Gurgling, Cracking, Rattling

Terminal Secretions: Treatment

- Repositioning for postural drainage
  - On side
  - Semi-prone
- Medication therapy
  - Anticholinergics
  - MOA:
    - Relax bronchial muscles and open airways
    - Dry mucous secretion and slow ciliary passage

Strickland, JM. Palliative Pharmacy Care, 2009.
Treatment: Anticholinergics

- Anticholinergic drugs are divided into:
  - Tertiary: cross blood brain barrier (BBB)
  - Quaternary: do not cross BBB
- Implications on side effect profile
- Bind muscarinic receptors

Anticholinergic Toxicity

- Dry skin
- Dilation
- Delirium
- Dysrhythmias
- Hypertension
- Tachycardia
- Hyperthermia
- Blurred vision
- Mydriasis
- Ileus
- Psychosis
- Confusion

Treatment Options: Anticholinergics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose/Route</th>
<th>Titration</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>1% eye drops</td>
<td>PRN</td>
<td>• Crosses BBB • Increased risk of CNS side effects</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>patch (1.5 mg base delivers 3 mg drug)</td>
<td>every 72 hours</td>
<td>• Crosses BBB • Onset 6 to 8 hours • Steady-state at 24 hours</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>0.3 mg q 8 hours P.O.</td>
<td>Up to every 6 hours</td>
<td>• PO absorption erratic • Can be given SubQ</td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>0.125 mg or 0.25 mg PO PRN</td>
<td>Up to every 6 hours</td>
<td>• Crosses BBB • Onset 30 min • Available in SL tablets</td>
</tr>
</tbody>
</table>
Pharmacodynamics: Anticholinergic Therapy

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Likar et al, 2008</th>
<th>Hugel et al, 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal cancer/cognitive dysfunction</td>
<td>Randomized, no placebo n = 32</td>
<td>Effectiveness of symptom control in Liverpool Care Pathway n = 72 (36 in each arm)</td>
</tr>
<tr>
<td>Advanced cancer</td>
<td>Glycopyrrolate 0.4 mg every 6 hours versus subQ scopolamine HBr 0.5 mg every 6 hours</td>
<td>SubQ glycopyrrolate 0.2 mg versus subQ hyoscyamine HBr 0.4 SubQ followed by continuous subQ drug infusions</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Glycopyrrolate superior to scopolamine HBr 44% vs 22%</td>
<td>Full response in glycopyrrolate group versus 22% in hyoscine group</td>
</tr>
<tr>
<td>*Small sample size</td>
<td>*Observer bias, unbalanced populations</td>
<td></td>
</tr>
</tbody>
</table>

Patient Considerations: Anticholinergics

- Contraindications to anticholinergic use:
  - Closed-angle glaucoma
  - Ileus
- Caution in patients with pre-existing delirium

**Take Home Point #6:** When selecting an agent for terminal secretions, glycopyrrolate does not cross BBB and may result in less CNS effects

End of Life Symptoms

- Pain
- Delirium and anxiety
- Terminal secretions
- **Dyspnea**
End of Life: Dyspnea

- Described as:
  - Short of breath
  - Suffocating
  - Choking
  - Drowning

- Due to:
  - Increased respiratory hindrance
  - Abnormality of respiratory muscles
  - Increased ventilatory demand

Treatment: Dyspnea

- Goal: Decrease discomfort
- Non-pharmacologic strategies:
  - Improve air circulation
  - Breathing exercises
  - Positioning
- Medications
  - Opioids
  - Anxiolytics if anxiety related

Opioids for Dyspnea

- Improve sensation of breathlessness at low doses
- Exact mechanism unknown
  - Distinct from respiratory depression at high doses
- No advantage of inhalation therapy over PO/IV

**Take Home Point #7:** While most opioids may be help with dyspnea, methadone is not effective for this indication
Anxiolytics for Dyspnea

- Second-line agents for dyspnea
- Effective for patients with anxiety disorder
- Treatment of anxiety → ameliorate dyspnea
- Lorazepam may be given PO, SL, or SubQ

Take Home Point #8: Anxiolytics are not first line therapy for patients complaining of breathlessness


Standardizing Symptom Orders

- Wide variation exists in the palliative care delivered at End of Life
- Recent research has looked at Comfort Care Order Sets (CCOS)
- Purpose to facilitate comfort care interventions
- BEACON Trial, 2014:
  - Multimodal approach to end-of-life care increased comfort interventions
- Impact of Standardized Palliative Care Order Set of End of Life Care, 2011:
  - Addition of order set significantly improved adherence to accepted end-of-life interventions


Example of CCOS

- Acetaminophen 650 mg PO/PR q4h PRN T>101°F
- For constant pain, give _____ (suggest Morphine SR) at ____ PO BID
- For intermittent pain or shortness of breath give:
  - Morphine sulfate ____ mg PO q2h PRN (suggest starting at 5mg)
  - If NPO, give morphine sulfate ____ mg IV/IV q2h PRN (suggest starting at 5mg)
- For anxiety, give lorazepam 0.5 mg IV/PO q6h PRN
- For constipation, senna/docusate 2 tablets PO QHS
- For nausea/delirium, haloperidol 1 mg PO/IV q4h PRN
- For excessive secretions hyoscyamine 0.125 mg SL q4h PRN

What are the potential advantages to having an inpatient palliative care order set?

A. Less wait time for medications
B. May anticipate patient needs
C. Allow for focused care on communication
D. All of the above
What’s in my PXYIS?

<table>
<thead>
<tr>
<th>Opioids</th>
<th>BZDs</th>
<th>Anticholinergics</th>
<th>Neuroleptics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td></td>
<td>Lorazepam</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Concentrated PO solution: 8ACU</td>
<td>Injection: All floors</td>
<td>Injection: All floors</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Hydromorphone</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Injection: All floors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Fentanyl</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Injection: All floors except 5ACU and PSYCH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>PO solution: 1mg/mL</td>
<td>Injection: 10 mg/mL</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Lorazepam</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Concentrated PO solution: None</td>
<td>Injection: All floors</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Injection: All floors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Dialzepam</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Injection: All floors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Glycopyrrolate</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Injection: 8ACU, 8ICU</td>
<td>Injection: All floors</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Atropine</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Injection: Ophthalmic Soln: None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Scopolamine</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Patch: 5ICU, 6ACU, 8ACU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Hyoscine</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Elixir: None</td>
<td>Tablet (SL, chewable, PO): 8ACU</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Concentrated PO: NONE</td>
<td>Tablet: 5ACU, 6ACU, 8ACU, 9ACU, 9ICU</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Injection (lactate): All floors</td>
<td>Tablet: All floors</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>Tablet: 5ICU, 6ACU, 8ACU, 9ACU, 9ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Risperidone</td>
<td></td>
</tr>
<tr>
<td>Opioids BZDs Anticholinergics Neuroleptics</td>
<td>ODT: All floors except 5ICU, 9WEST</td>
<td>Tablet: All floors</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Current as of 3-16-15

Medication Orders

- Anticipatory orders especially important if:
  - Not stocked in PXYIS
  - STAT orders to be verified and sent by pharmacy within 1 hour
    - Do not call unless <1 hour
  - Routine orders to be verified and sent by pharmacy within 2 hours

Final Considerations

- End of life is an unpredictable process
- Evaluate patient’s comfort level bedside
- Medications are one part of the treatment
- Anticipating end-of-life needs may provide more timely care for patients
Thank You

Dr. Katie Stowers
Laurajo Ryan, PharmD
Bryson Duhon, PharmD

Questions?

Secret CE Codes

For Pharmacists: WG8i
For Technicians: k8iC